CREATING CLARITY

CKD vs AKI: So many markers, so little time, so much confusion!

Rebekah Mack DVM, DACVIM-SAIM, MSEd (Candidate)

IDEXX

Learning outcomes/ objectives

Section 1: Renal 101

- Recall essential components of kidney function
- Describe current kidney diagnostics and practical application in health and disease

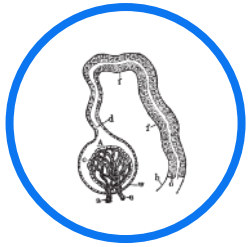
Section 2: Biomarkers in kidney disease

- Understand through a deeper dive how current markers assess function
- Resource literature and studies to develop best approaches to diagnosis of kidney disease, both AKI and CKD specifically

Kidney biomarker evolution

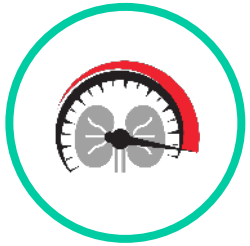
Proteinuria

Described by Hippocrates 400 B.C.



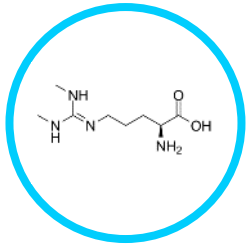
Creatinine

Jaffe reaction 1886



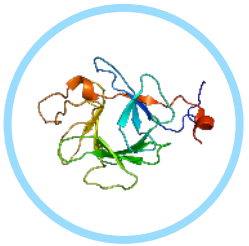
Glomerular filtration rate

Cockcroft-Gault equation for estimating GFR in 1973



SDMA

Validated for use in dogs 2015



FGF-23

Launched for felines with chronic kidney disease 2022

Urinary cystatin B

Detects both active and acute kidney damage

Launching Fall 2023

Diagnosing kidney disease is more than diagnostics

Physical exam

Kidney palpation
Muscle mass
Cardiac auscultation

Medical history

Appetite/weight loss
Energy
Water consumption

Diagnostics: lab work

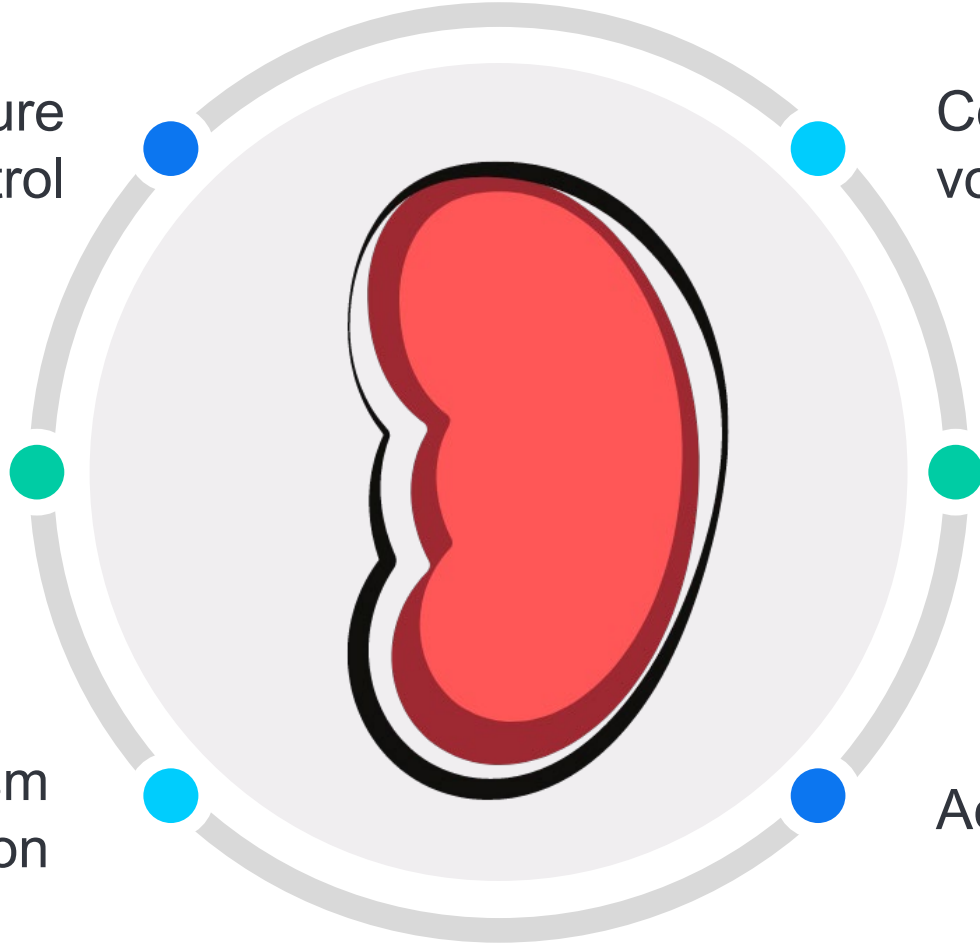
Chemistry
CBC
Urinalysis

Imaging

Radiographs
Ultrasound

Clinical decision points

Kidney function is essential to well-being



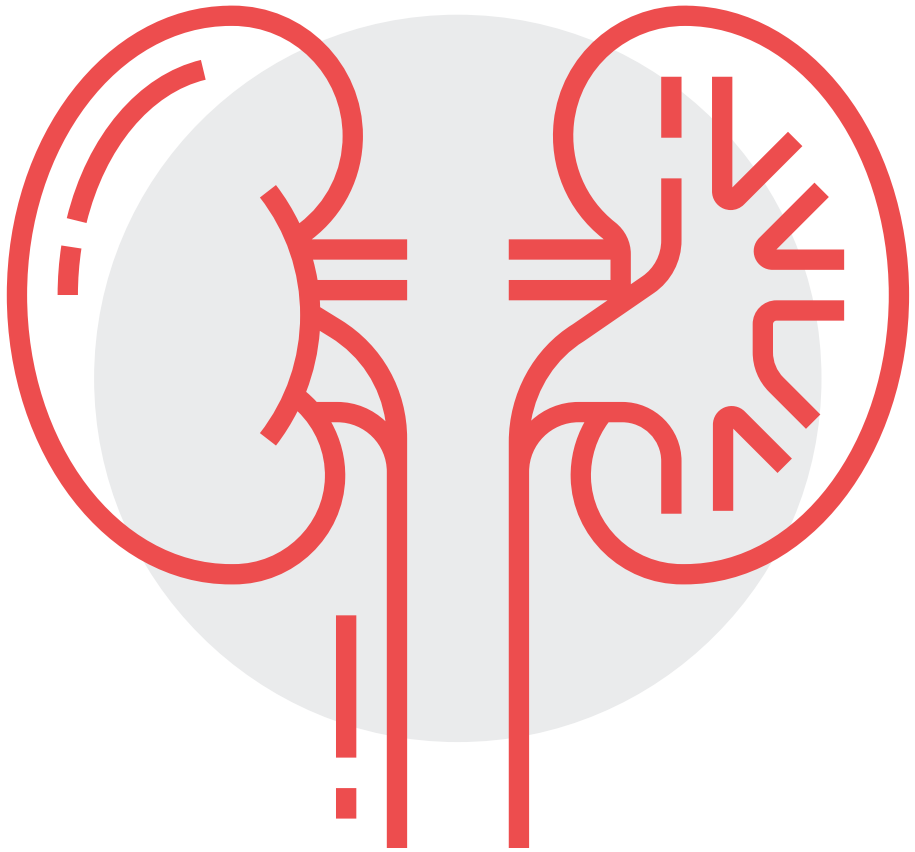
Kidney function is essential to well-being

Prevalence

- CKD in cats rises sharply with age, with an estimated prevalence of <1% in young cats, 30-40% in cats over 9 yoa and 60% in geriatric cats
- Dogs 0.02-0.4% reported prevalence—likely higher than reported if consider proteinuria

Causes for morbidity and mortality

- Trauma
- Gastrointestinal
- Lower urinary tract problems
- Renal disorder
- Non-specific illness
- Neoplasia, mass lesion disorders



Conroy M, Brodbelt DC, O'Neill D, Chang Y-M, Elliott J. Chronic kidney disease in cats attending primary care practice in the UK: a VetCompass TM study. Veterinary Record. 2019;184(17):526-526. doi:10.1136/vr.105100
Lulich JP, Osborne CA, O'Brien T, Polzin DJ. Feline renal failure: questions, answers, questions. Compendium on Continuing Education for the Practicing Veterinarian. 1992;14:127-152.
Marino CL, Lascelles BDX, Vaden SL, Gruen ME, Marks SL. Prevalence and classification of chronic kidney disease in cats randomly selected from four age groups and in cats recruited for degenerative joint disease studies. Journal of Feline Medicine and Surgery. 2014;16(6):465-472. doi:10.1177/1098612X13511446
Sparkes AH, Caney S, Chalhoub S, et al. ISFM Consensus Guidelines on the Diagnosis and Management of Feline Chronic Kidney Disease. Journal of Feline Medicine and Surgery. 2016;18(3):219-239. doi:10.1177/1098612X16631234
Egenvall A, Bonnett BN, Häggström J, Holst BS, Möller L, Nødtvedt A. Morbidity of insured Swedish cats during 1999–2006 by age, breed, sex, and diagnosis. Journal of Feline Medicine and Surgery. 2010;12(12):948-959. doi:10.1016/j.jfms.2010.08.008

Categories of biomarkers and analytes to measure kidney function

Indirect markers of function

Limited extrarenal effect:

+ SDMA
+ Creatinine

More extrarenal effect:

+ Phosphorus
+ BUN

Urine-based markers

Urinalysis

+ Physical, chemical sediment

UPC

+ Proteinuria

Other important analytes

+ Potassium
+ Sodium/chloride
+ Calcium
+ Albumin/TP
+ Hematocrit
+ FGF-23

Acute kidney injury markers

+ Cystatin B
+ NGAL
+ Urine clusterin

You need broad assessment to understand kidney health.

What can we measure in clinical practice?

Functional markers

Represent the blood flow and clearance rate of the kidneys

Creatinine, SDMA, BUN

Impacted by primary and secondary diseases of the kidney

Chronic disease to acute disease; other metabolic disease

Tubular function

Important in solute management and water management (i.e., urine concentration)

Electrolytes, glucose, pH of blood

Impacted by primary and secondary diseases of the kidney

Any disease that impacts the ratio of solutes in the urine and the function of transmitters in the tubules

Urine production

Concentration and dilution abilities, disease of the urinary tract, reflection of systemic disease

Concentration/volume, pH, crystalline and noncrystalline, protein

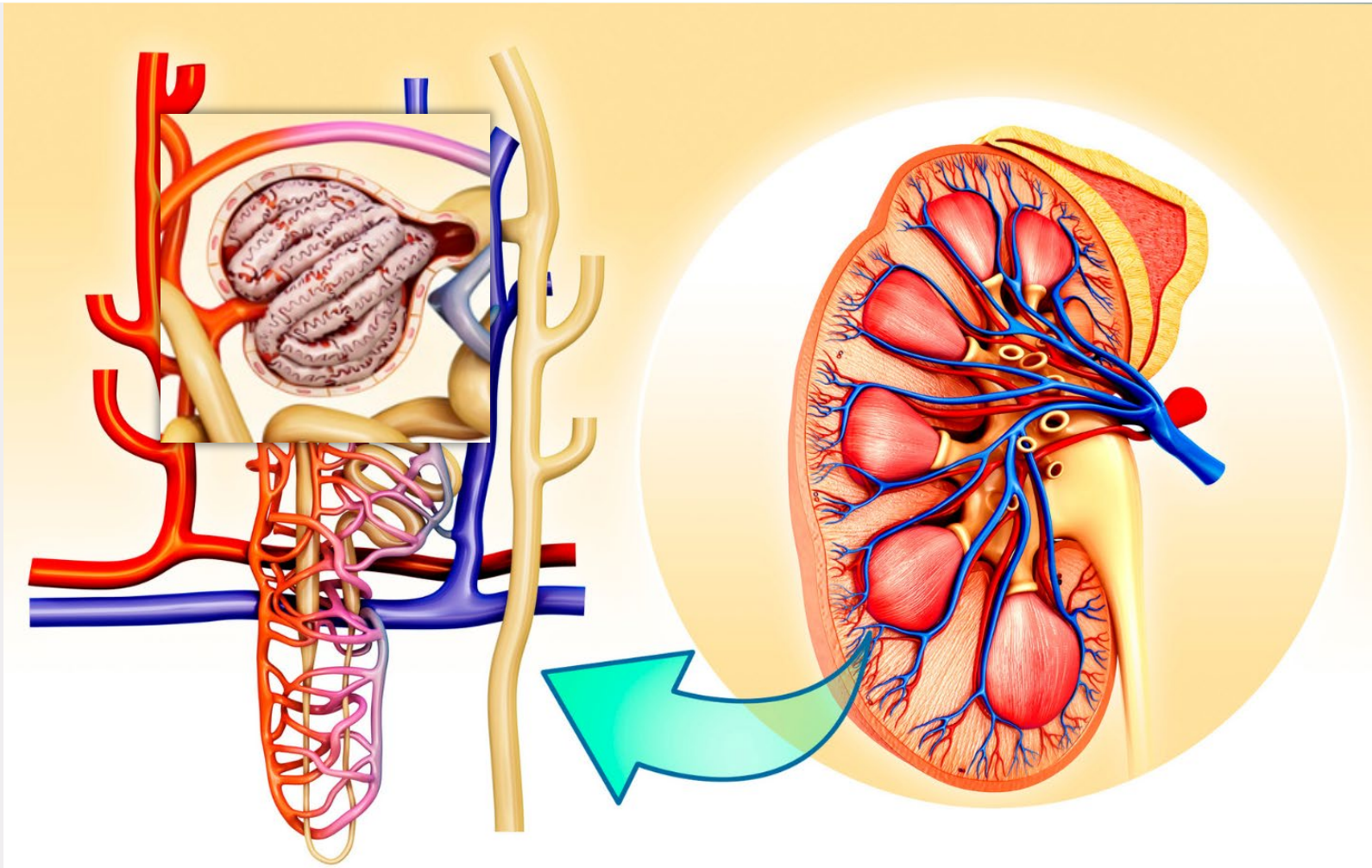
Impacted by primary and secondary diseases of the kidney

Chronic disease to acute disease; other metabolic disease

What can we measure in clinical practice?

Functional markers

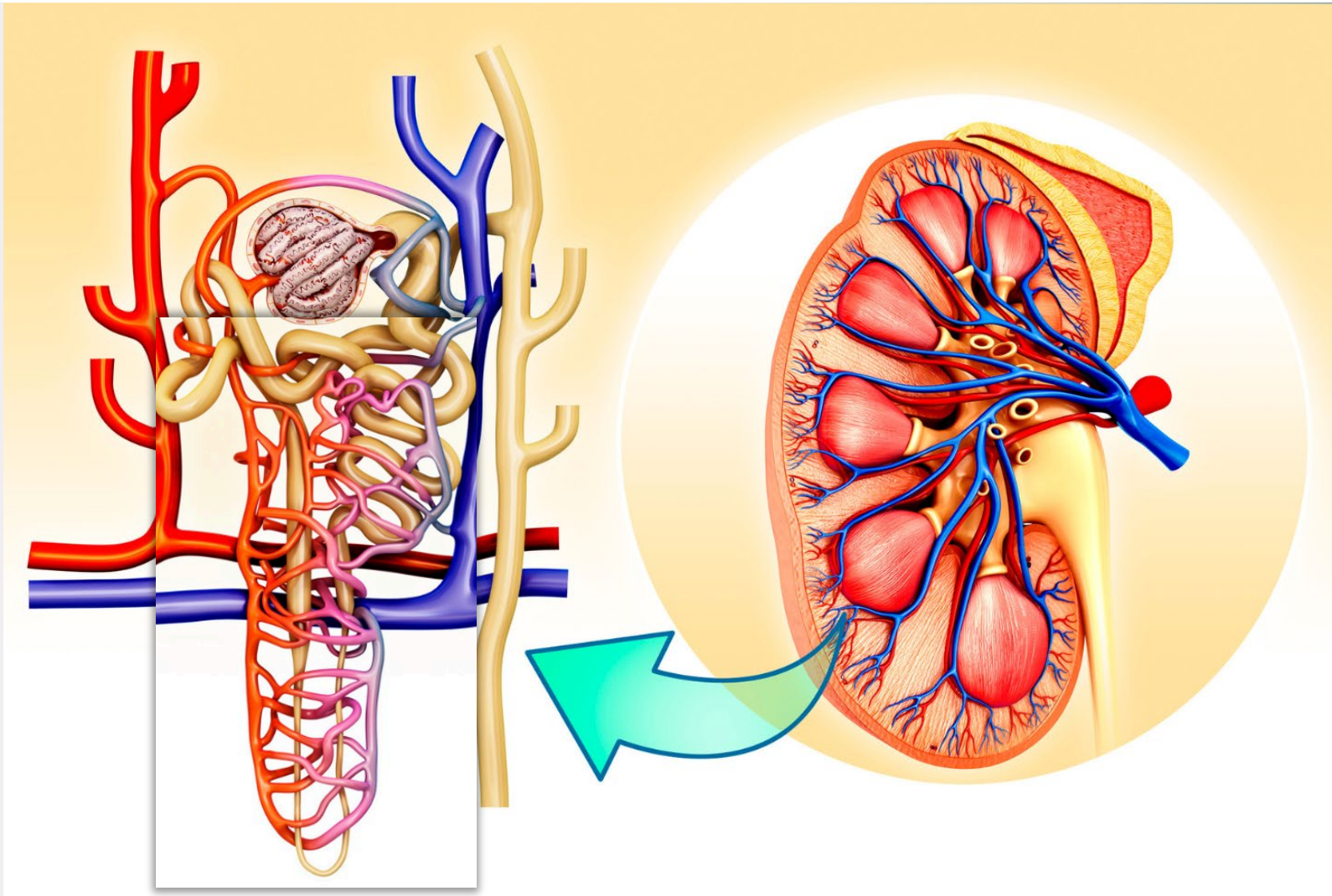
+ Glomerulus is the primary site associated with glomerular filtration rate (GFR)
+ GFR is used as a surrogate for kidney function and filtration



What can we measure in clinical practice?

Tubular function

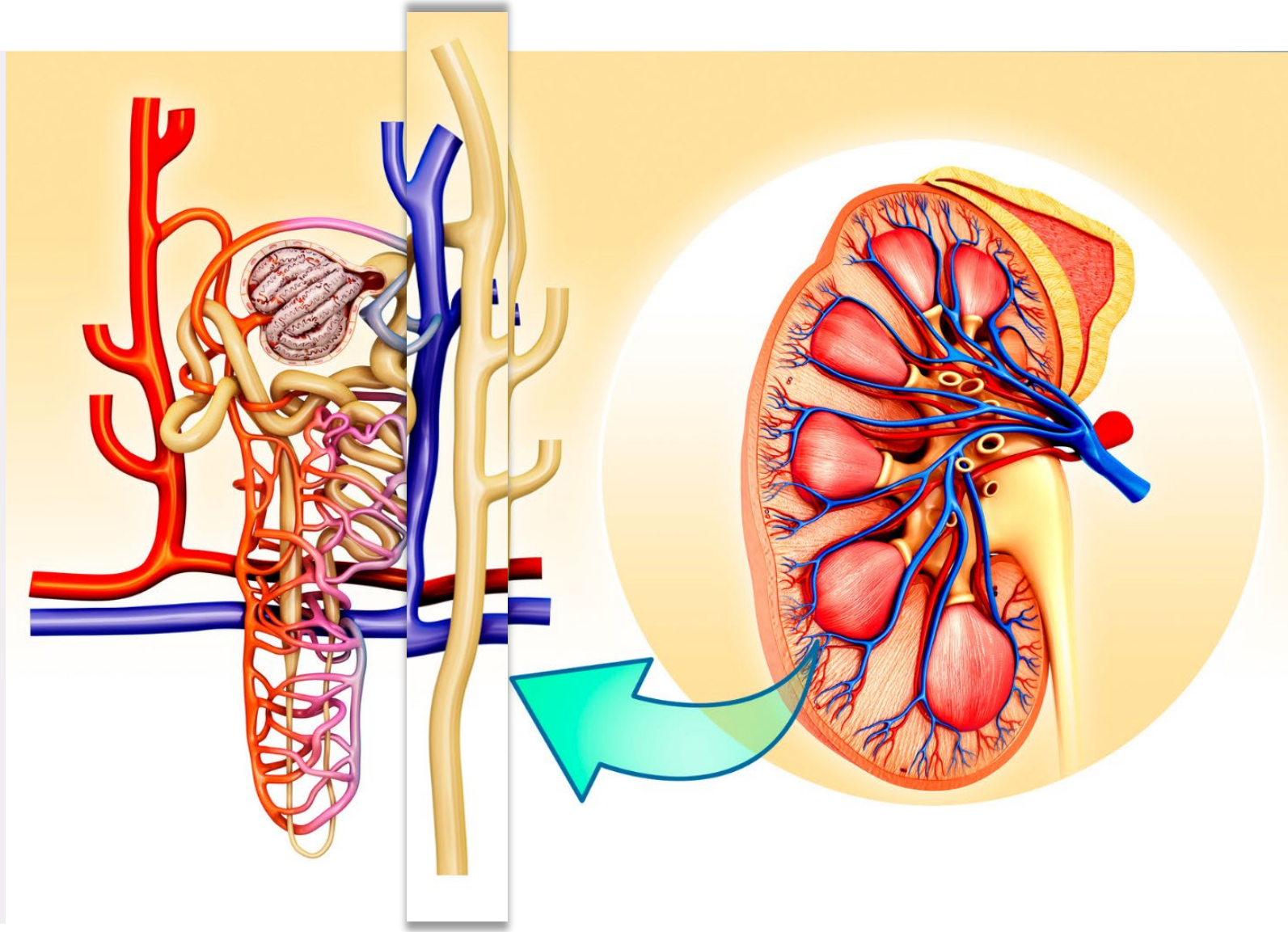
- The actual work of the kidney primarily takes place here: filtering, reabsorbing, and secreting solutes and water
- Impact urine concentration and what is excreted—dysfunction can impact electrolytes, protein levels, glucose, acid-base balance
- Indirectly captured in chemistry panel and urinalysis



What can we measure in clinical practice?

Urine composition

- Urine can reflect the functional capacity of the kidneys through concentration, systemic health, and disease of the urinary system
- Presence of protein, changes in solutes, concentration, and active sediment
- Urinalysis—physical, chemical, and sediment exams. Capture important information about systemic health, as well as specific to kidney health.
- Urine protein:creatinine (UPC) ratio



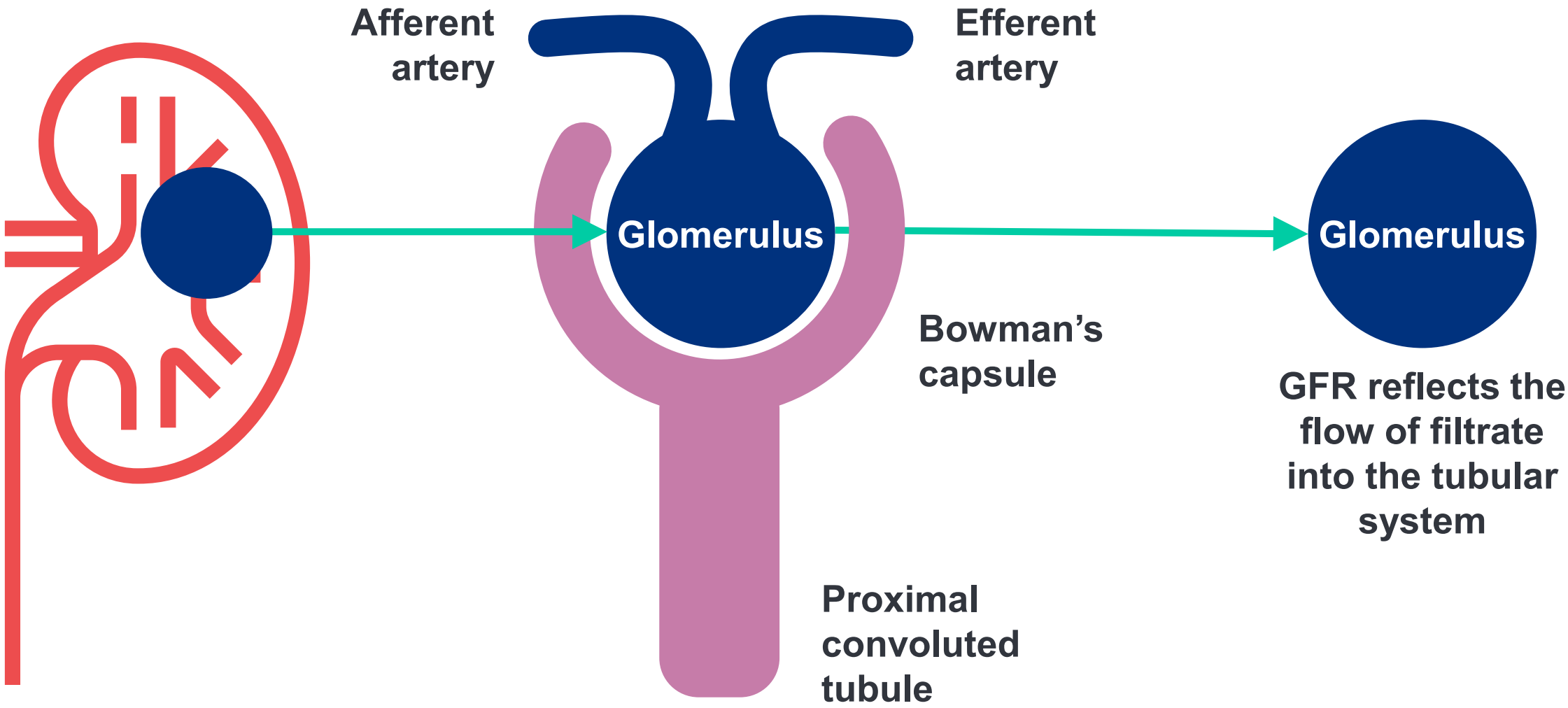
My lightbulb moment for understanding GFR

Volume of blood in the animal, i.e., dehydration or volume expansion with fluids

Rate at which blood is moving into the kidney and glomerulus, i.e., hypertension

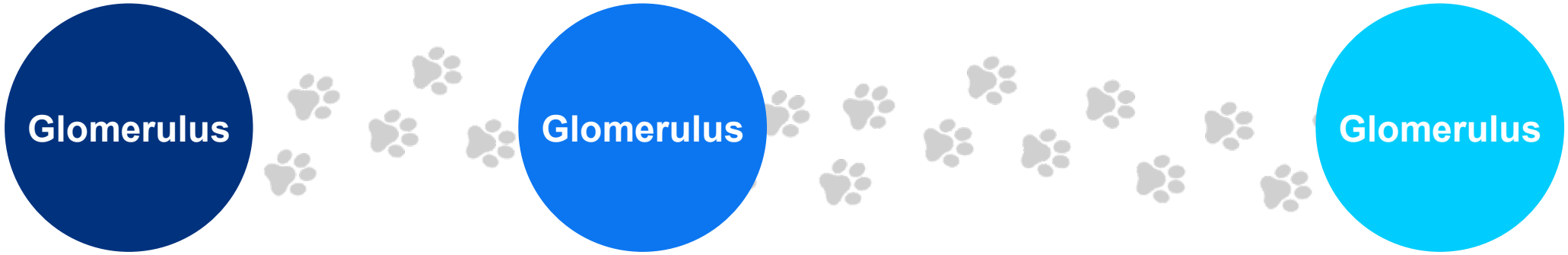
The size of the cat or dog, i.e., larger has lower and smaller has higher baseline GFR

GFR: Brief review of physiology and influences



Bartges J, Polzin D, eds. Nephrology and Urology of Small Animals. 1st ed. Ames, IA: Wiley-Blackwell; 2011.

Clinical choices reflect quality testing, convenience, and cost



GFR reflects the flow of filtrate into the tubular system

Measure with lohexal or Inulin

Measure with indirect markers

Creatinine, SDMA, BUN

What is missing in our evaluation of the nephron?

*Hint: Nephron = Glomerulus + **Tubules**

Tubular function and the markers that reflect general function

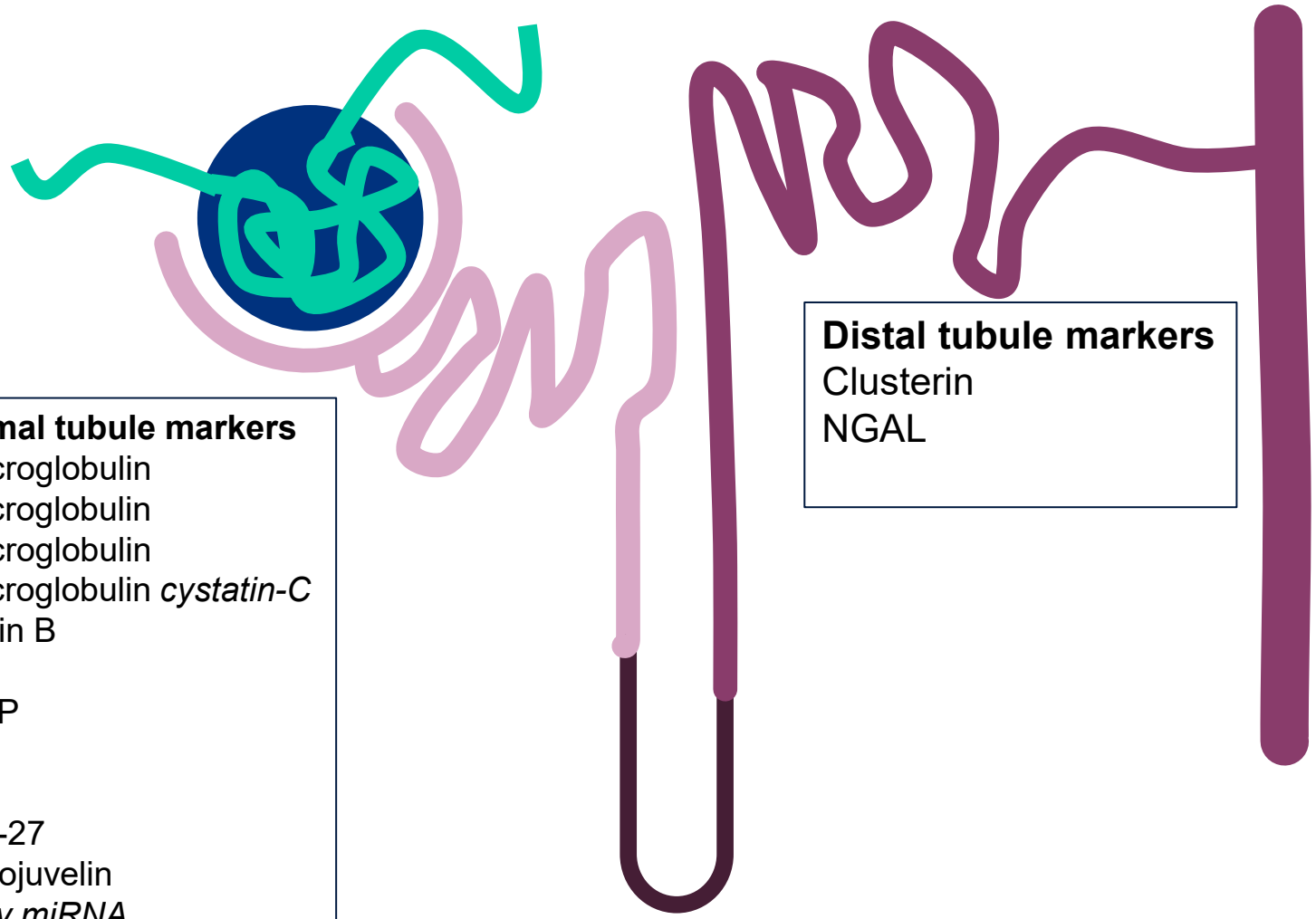
Filtration, reabsorption, and excretion rates of different substances by the kidneys

	Amount filtered	Amount reabsorbed	Amount excreted	% of Filtered load reabsorbed
Glucose (g/day)	180	180	0	100
Bicarbonate (mEq/day)	4320	4318	2	>99.9
Sodium (mEq/day)	25,560	25,410	150	99.4
Chloride (mEq/day)	19,440	19,260	180	99.1
Potassium (mEq/day)	756	664	92	87.8
Urea (g/day)	46.8	23.4	23.4	50
Creatinine (g/day)	1.8	0	1.8	0
SDMA (mg/dL)				

In health we expect no GLU

Freely filtering no- nominal active reabsorption

Kidney injury markers with some translation or veterinary data, multiple applications in CKD and AKI



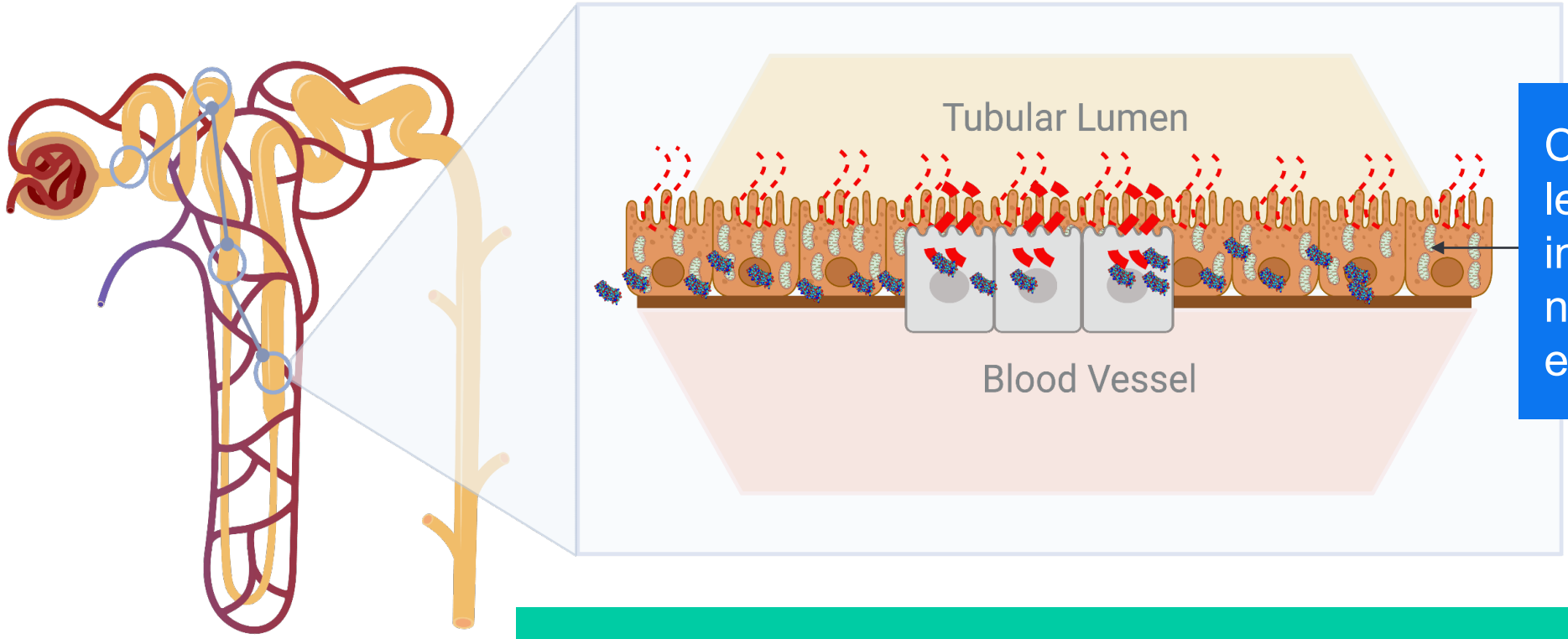
Proximal tubule markers
α1-microglobulin
β2-microglobulin
α1-microglobulin
β2-microglobulin *cystatin-C*
Cystatin B
KIM-1
L-FABP
NGAL
RBP
UHSP-27
u-hemojuvelin
Urinary miRNA

Distal tubule markers
Clusterin
NGAL

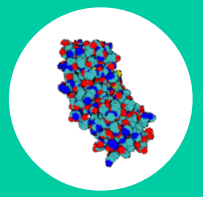
Biomarker	Dog	Cat	Assay
Cystatin B Urine	✓	✓	Immuno assay
NGAL Serum Urine	✓	✓	ELISA
Kim-1 Urine	✓	✓	Immunoa ssay
L-FABP Serum Urine	✓	✓	ELISA
Clusterin Urine	✓	✓	Immunoa ssay ELISA
UHSP-27 Urine	✓	✓	ELISA

+ U(biomarker) creatinine ratio is common
+ Multiplex panels versus ELISA stand alone

During **active or acute injury** to the kidney, the cells along the lining of the tubule system (responsible for secretion and reabsorption of solutes and water) can be damaged or necrotic.

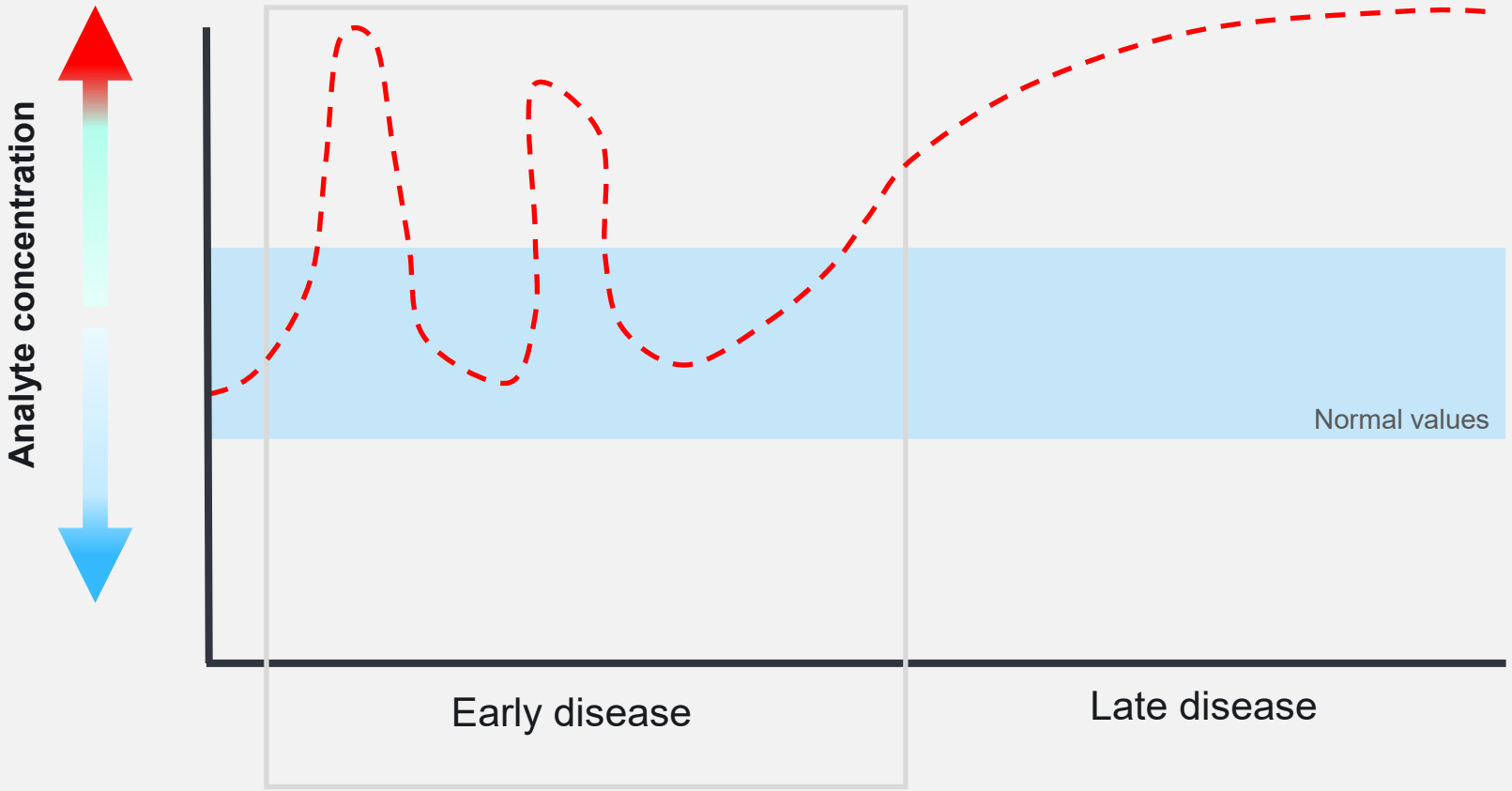


Cystatin B leakage from injured or necrosed tubular epithelial cells



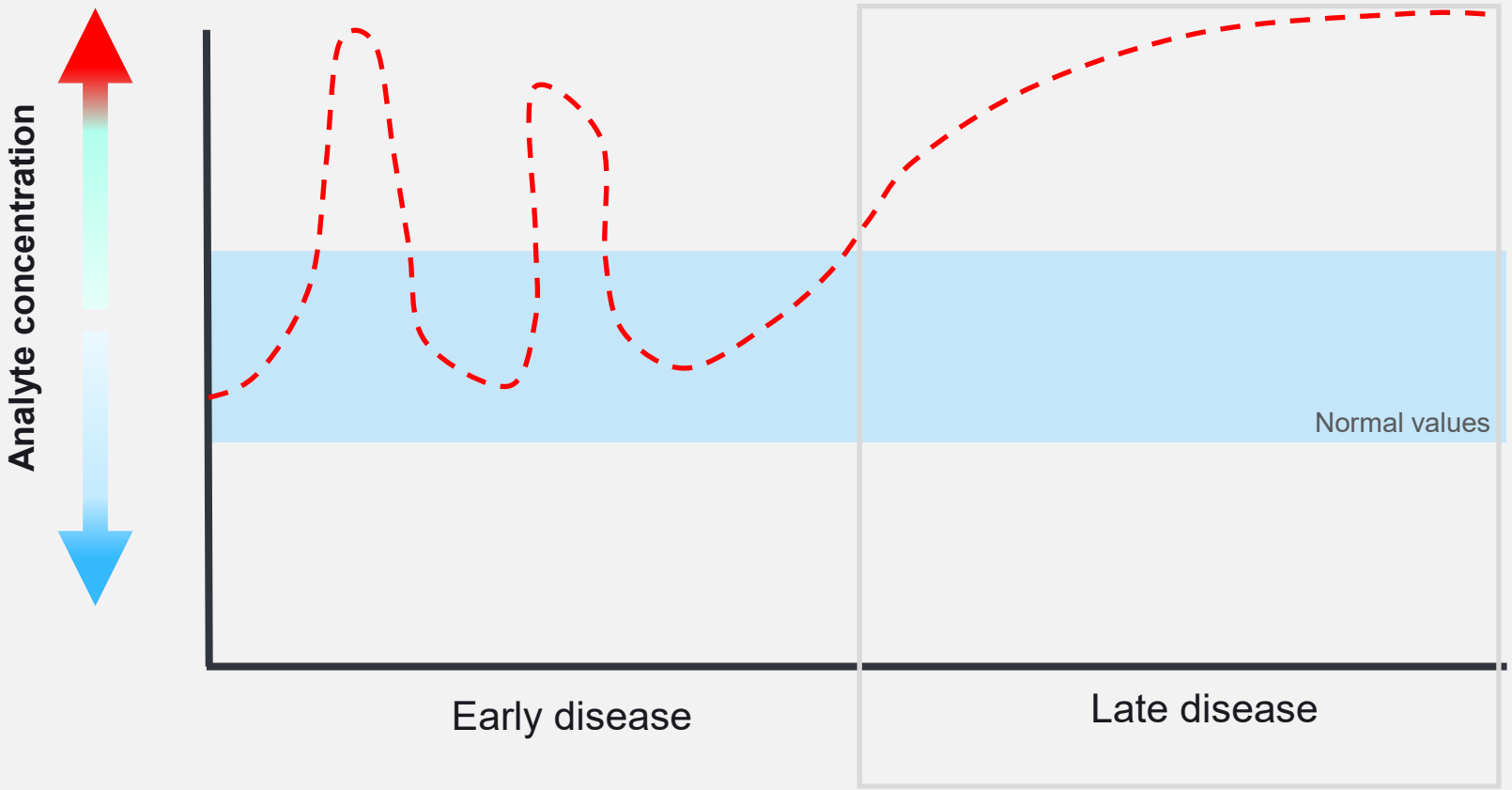
Increased cystatin B can occur with or without functional marker increase, alerting to earlier, ongoing, and unresolved injury to the kidney.

Tubular injury markers – suggested to have two phases



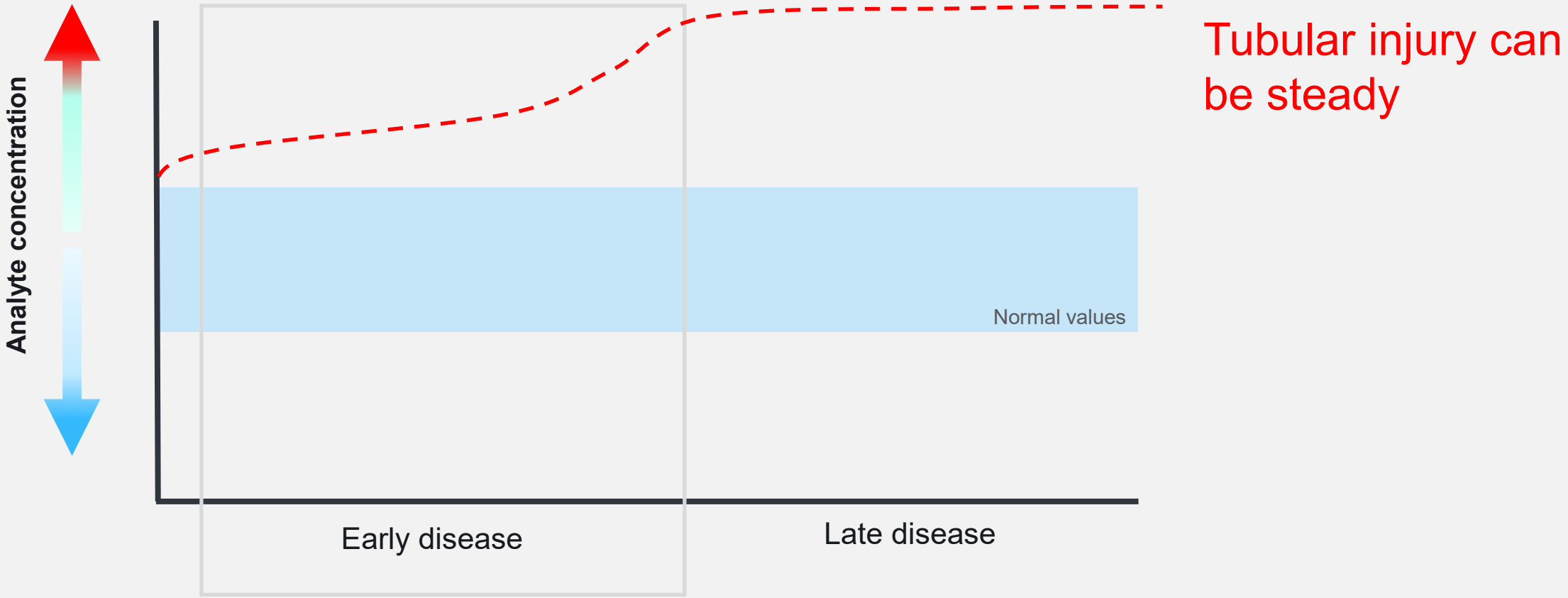
Early tubular injury

Tubular injury markers – suggested to have two phases

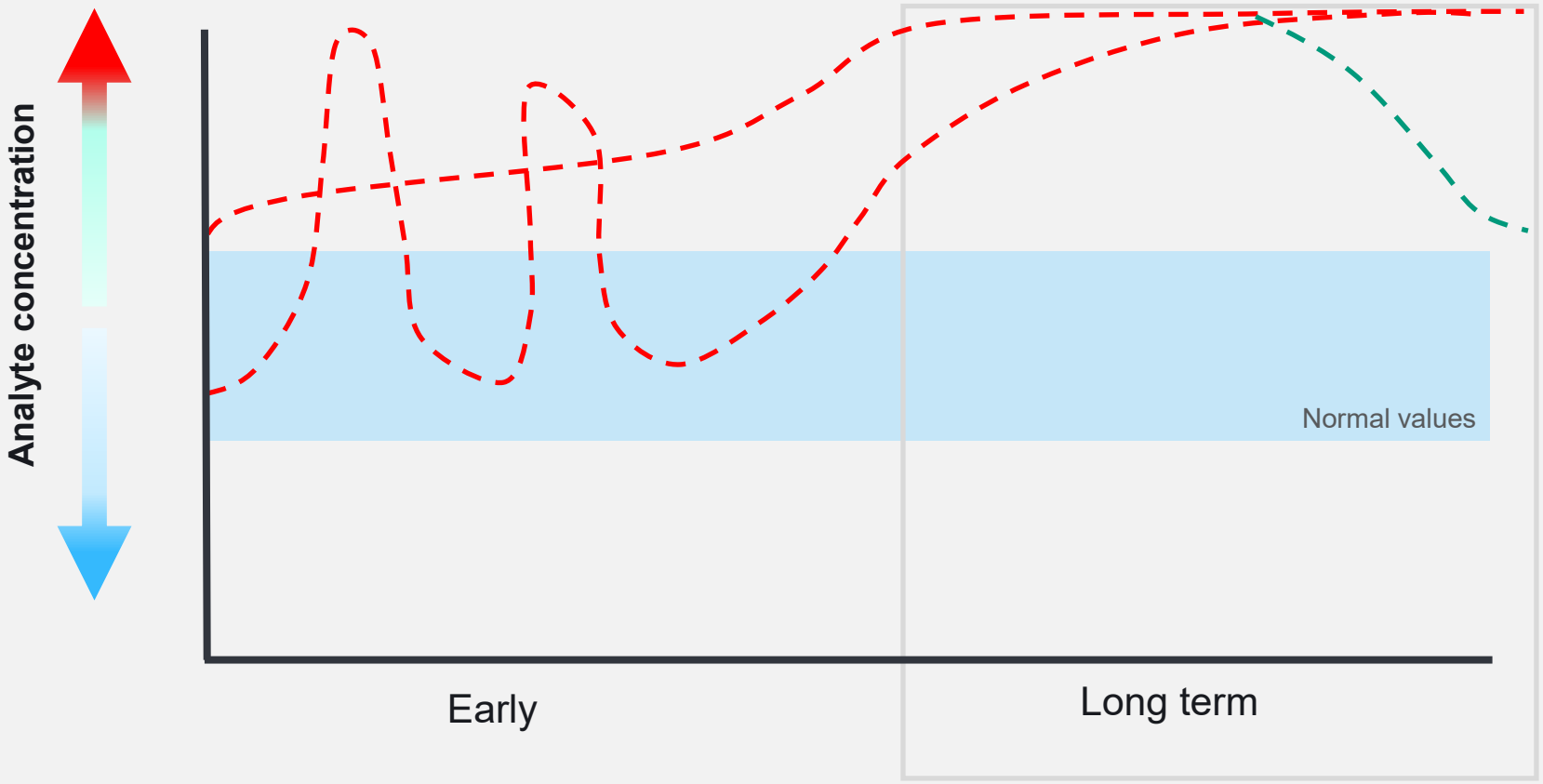


Late in tubular injury

Tubular injury markers – steady rise may occur

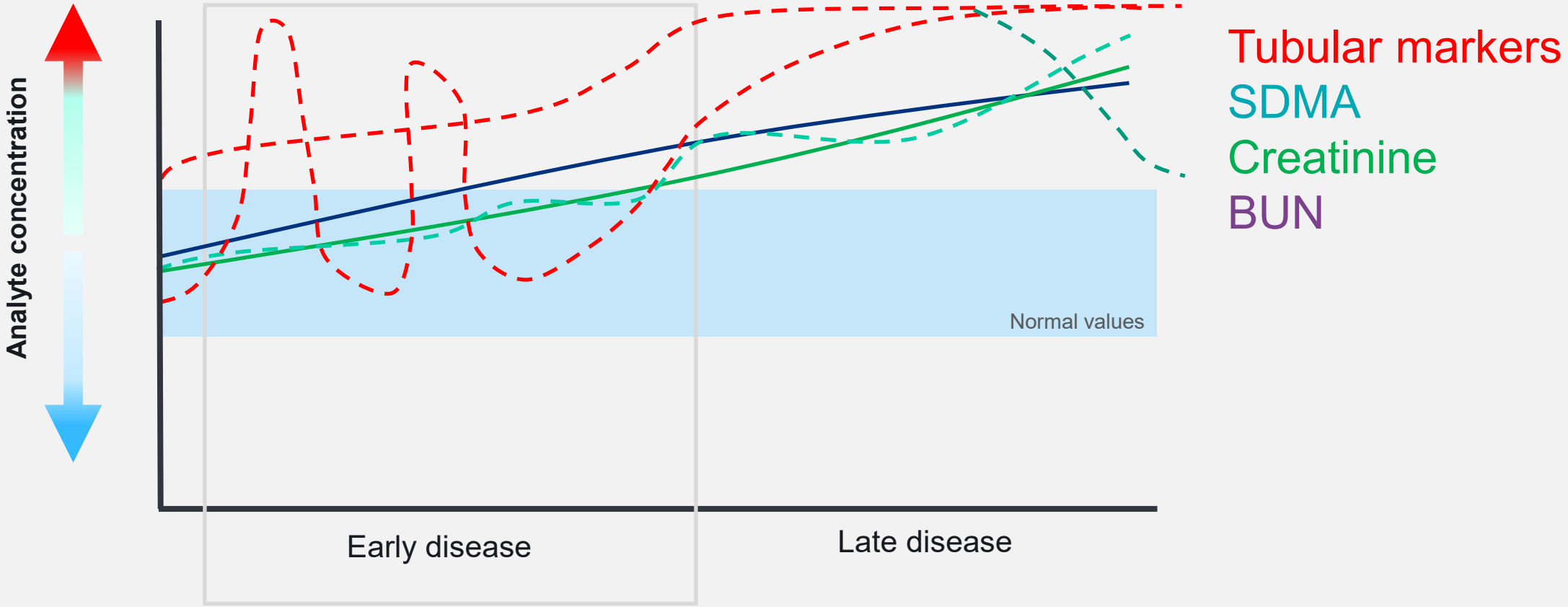


Trajectories of tubular injury markers are often individualized to disease and patient and may not apply well to large populations

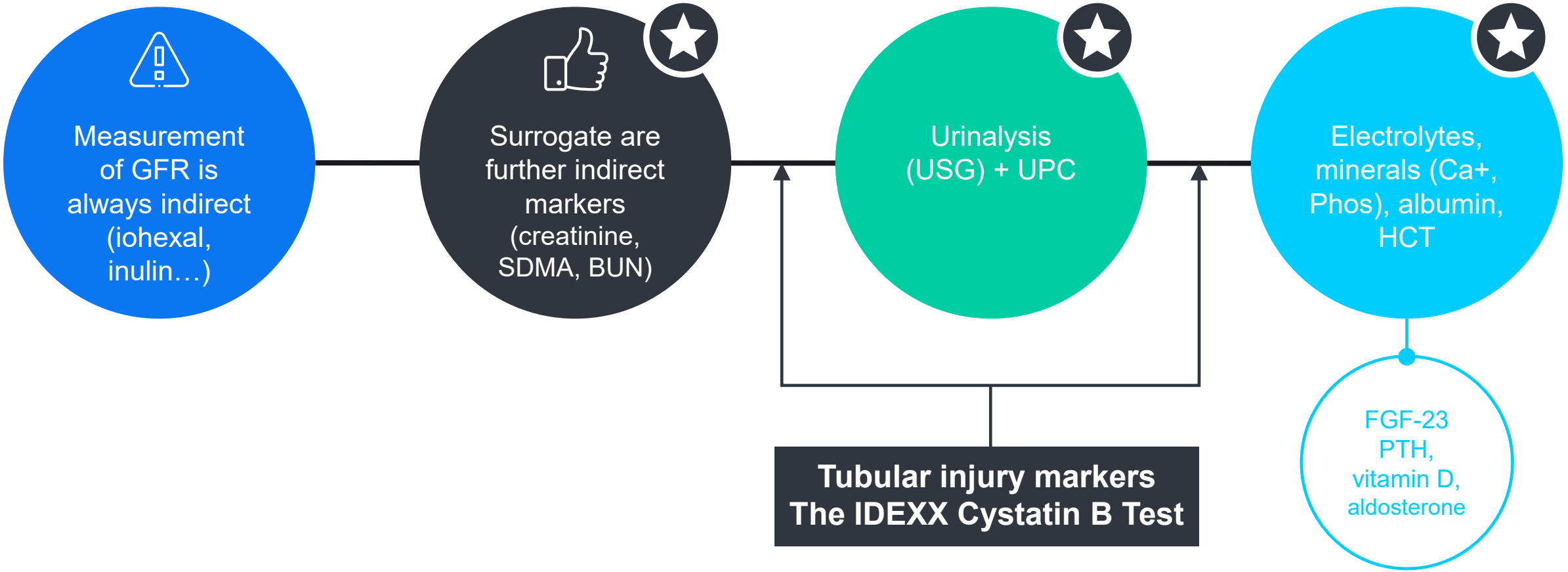


Tubular injury
Loss of production due to cellular reduction

Kidney injury markers could be additive to current indirect functional markers



Kidney function is defined by understanding GFR and the methods in which we measure it in clinical practice



Best use case for renal biomarkers

Use every tool you have!

- How often does a biomarker have to aid in diagnosis to be used as a screening test?
- **Think about limitations:**
  - Creatinine: muscle mass, early disease
  - SDMA: rare comorbidities
  - Tubular injury markers: the IDEXX Cystatin B Test (Fall 2023)
  - FGF-23: feline CKD management
  - USG: comorbidities
  - Proteinuria: comorbidities
- Even with limitations, often by using all of the available diagnostics you can put the puzzle together.

Section: Understanding the era

Kidney function and disease is defined by risk factors, injury, and outcomes

Risk factors

Breed

Age

Sex

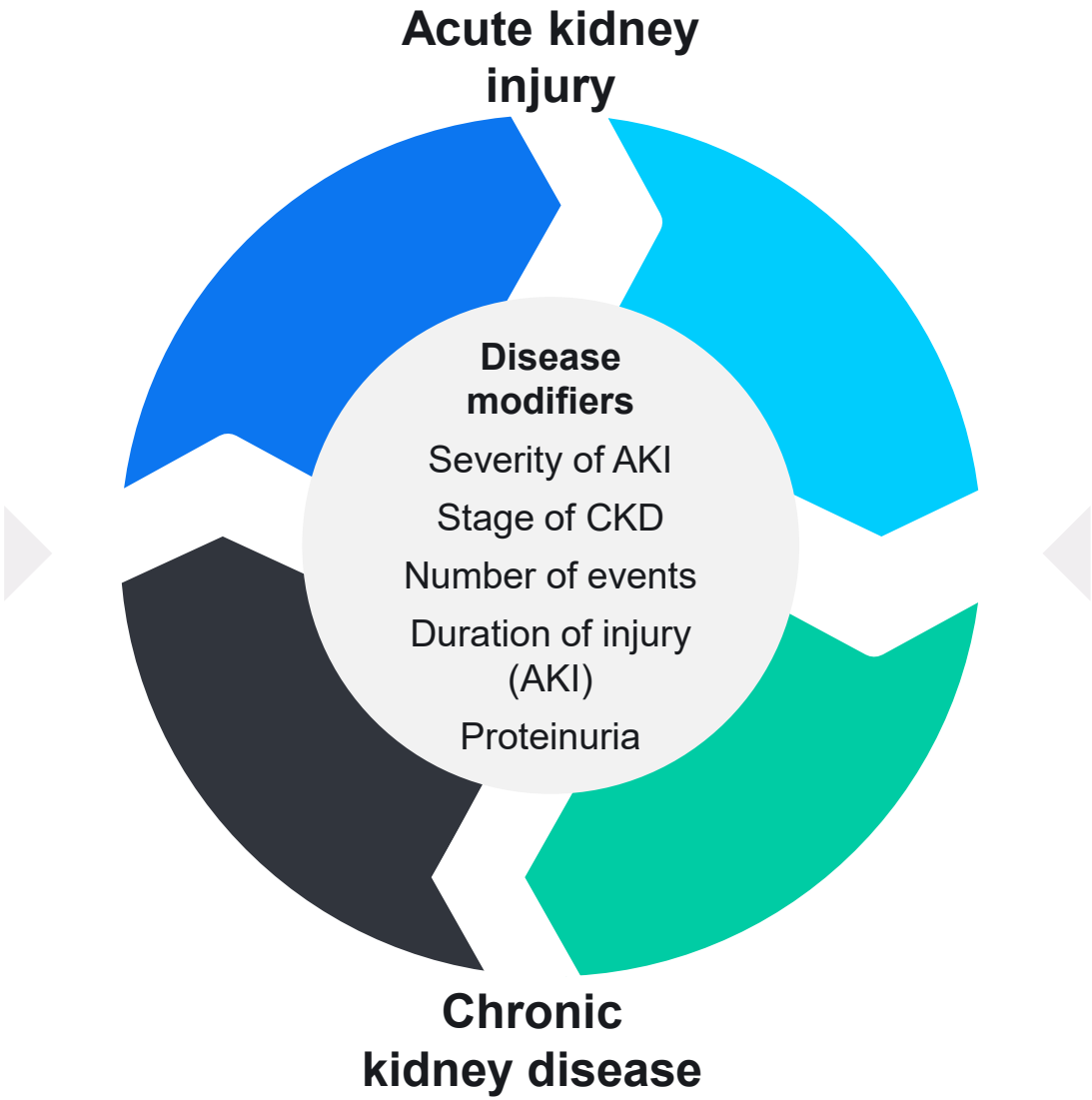
Diet

Drugs

Hypertension

Metabolic disease

Cardiac disease



Outcomes

Cardiovascular events

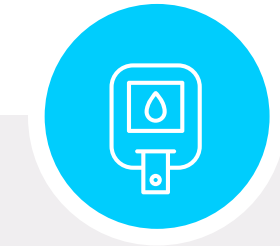
Kidney events

Diminished quality and quantity of life

Cost events

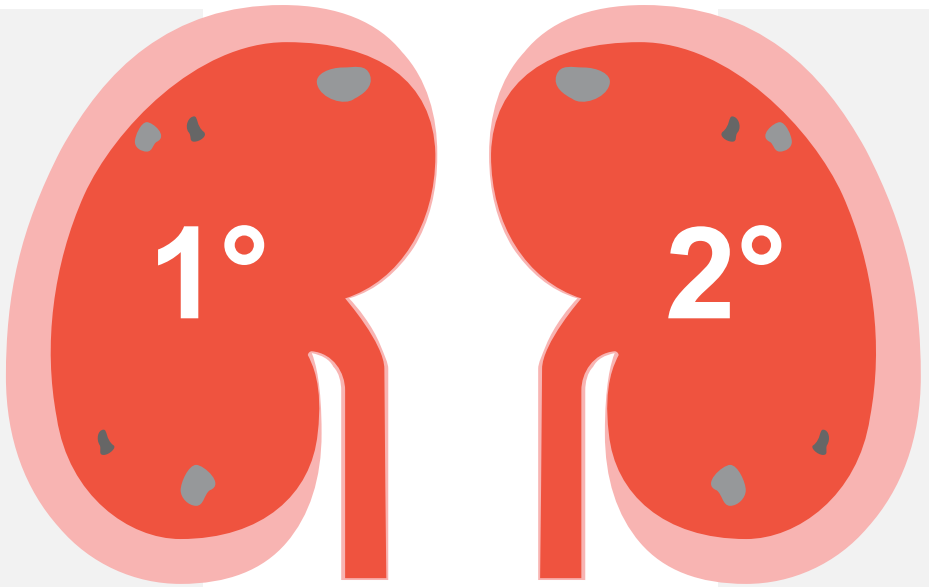
Source: Chawla LS, Eggers PW, Star RA, Kimmel PL. Acute kidney injury and chronic kidney disease as interconnected syndromes. N Engl J Med. 2014;371(1):58–66. doi:10.1056/NEJMra1214243

Comorbidities or disease states can heavily impact kidney health

 **Heart disease**	 **Liver disease**	 **Gastrointestinal disease**	 **Endocrinopathy**	 **Infectious**
Cardiorenal or renocardiac syndrome	Hepatic disease, congestion	Inflammatory effect, hypoproteinemia	Hormone imbalance, catabolic state	Inflammatory/ immune acute or chronic
NT-proBNP Troponin SDMA	CRP Iron	CRP Microbiome	Aldosterone PTH Vitamin D Iron	Regional infectious testing Leishmaniasis Ehrlichiosis Lyme disease

Take the time to determine primary versus secondary kidney insults

+ Idiopathic or unknown causes of CKD
+ Congenital disease
+ Immune-mediated glomerular disease

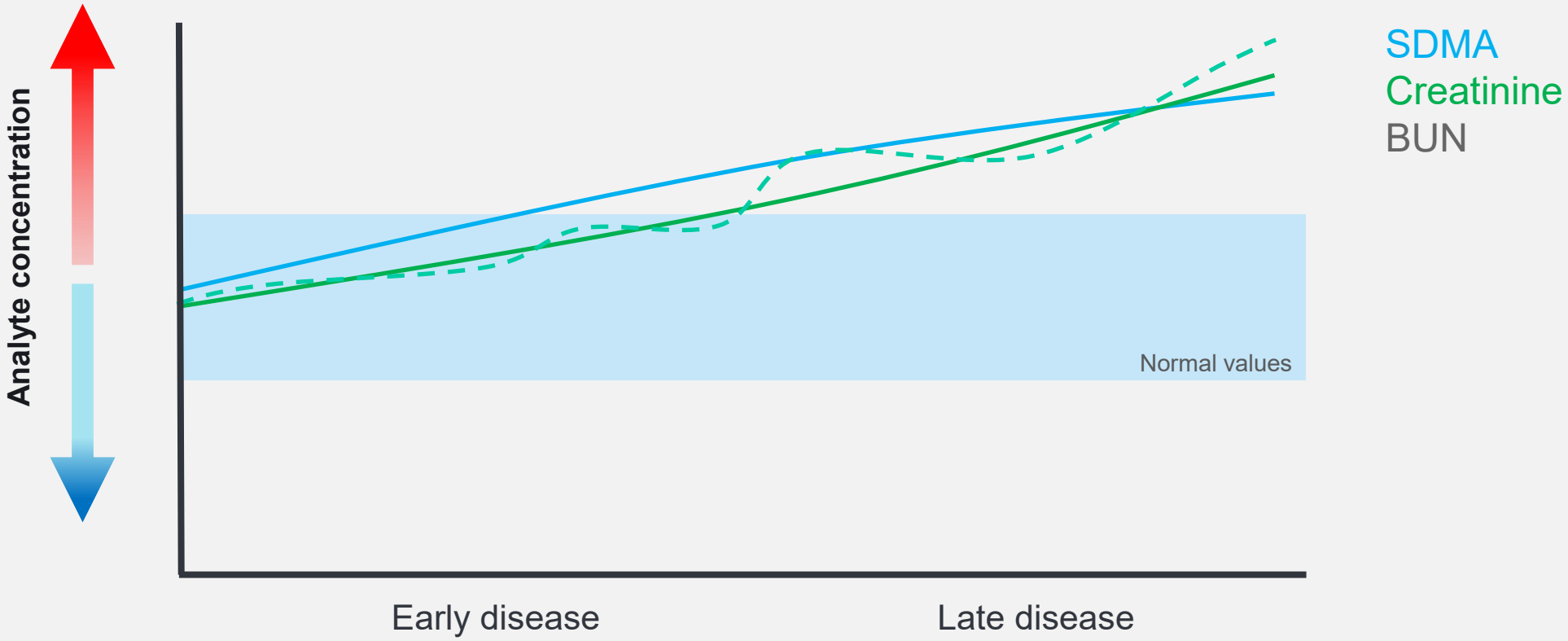


+ Toxicity
+ Vector-borne disease
+ Pyelonephritis
+ Obstructive disease
+ Neoplasia
+ Sepsis

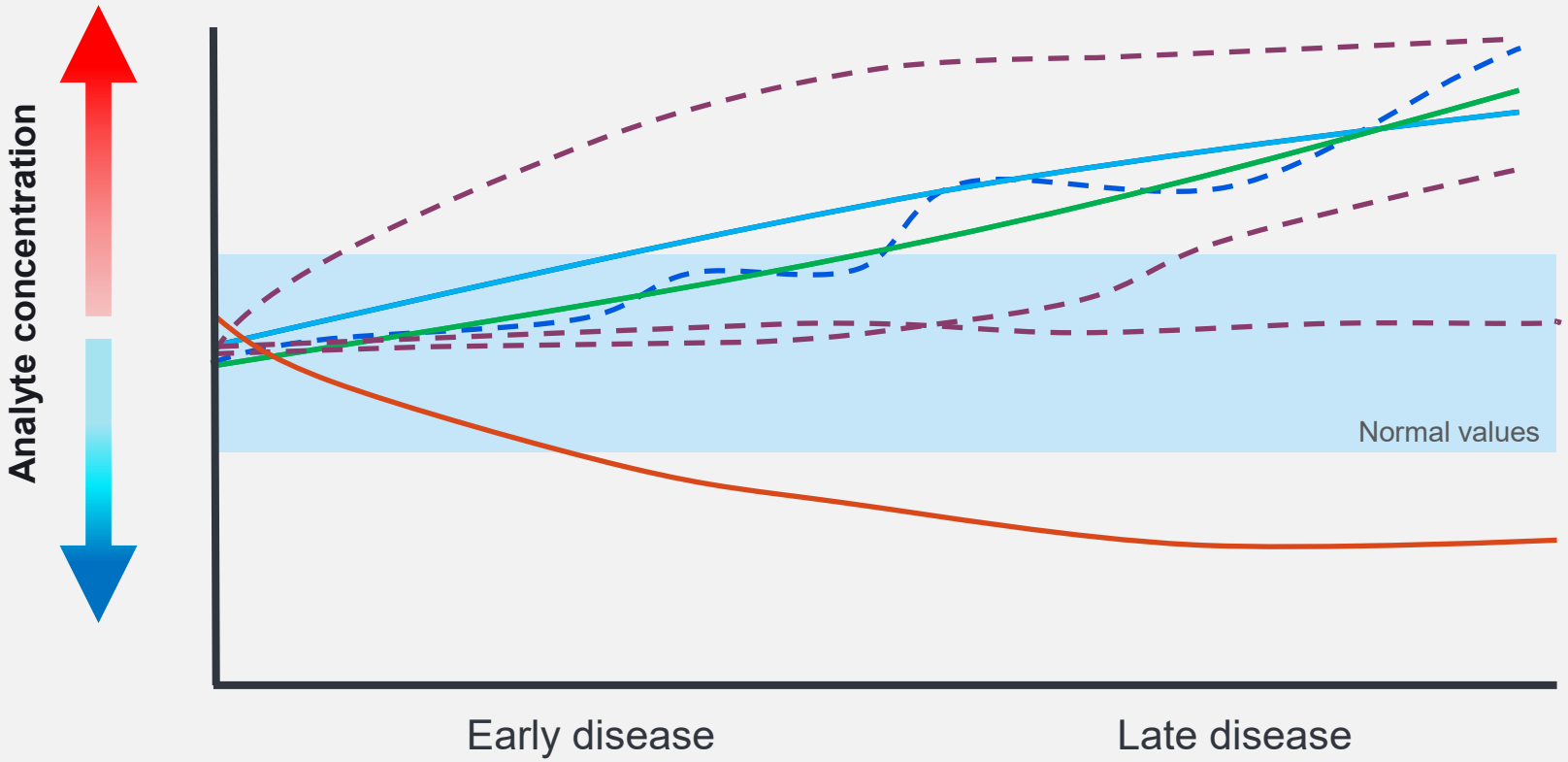
Knowing this determines

- Needed diagnostics
- Prognosis
- Treatment options

Traditional indirect functional markers are the current mainstay of kidney diagnostics



Traditional indirect markers benefit from measurement of USG and urine protein levels



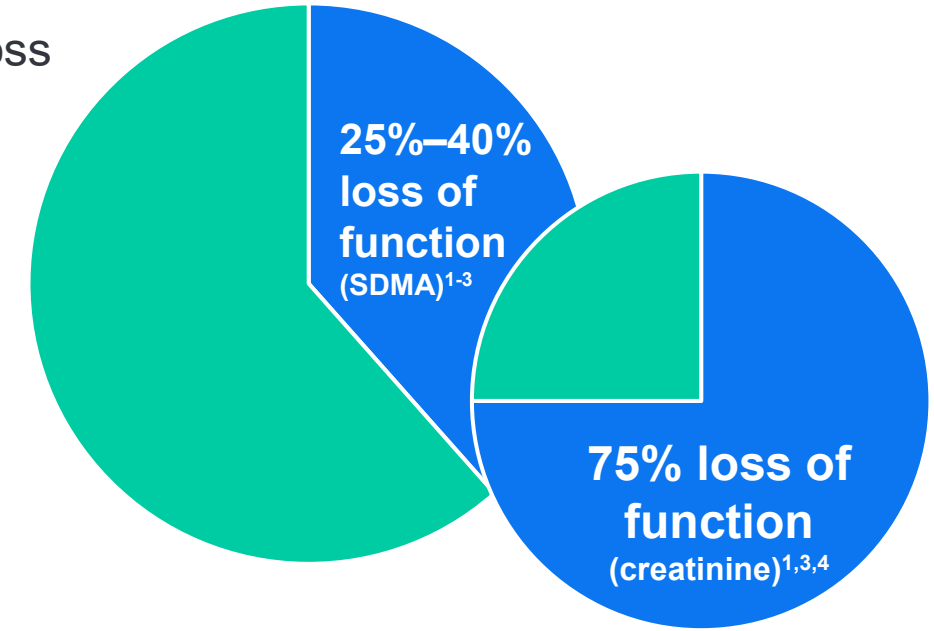
Proteinuria (multiple trajectories in disease)
USG
SDMA
Creatinine
BUN

Cystatin B partners with existing kidney biomarkers to give the most complete view of kidney disease.

Current functional markers

SDMA and creatinine

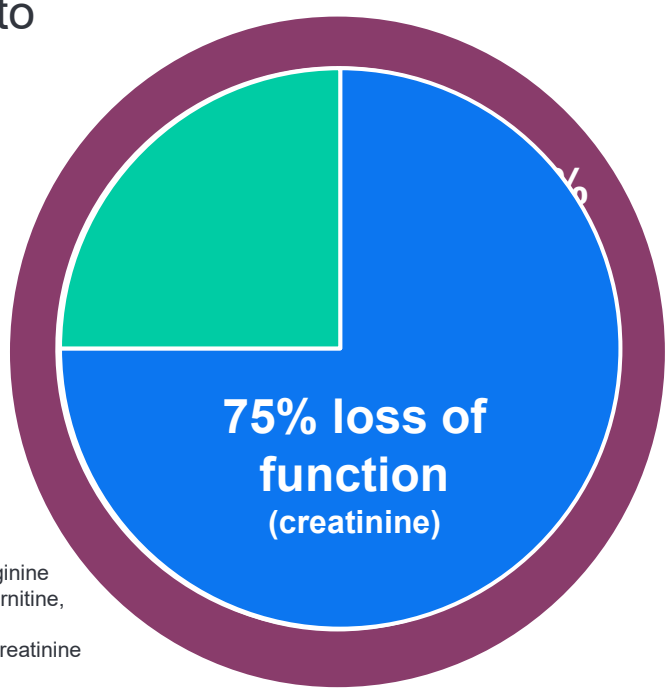
Indicate loss of GFR or decline in kidney function



Active kidney injury marker

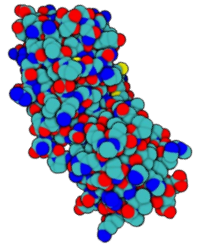
Cystatin B

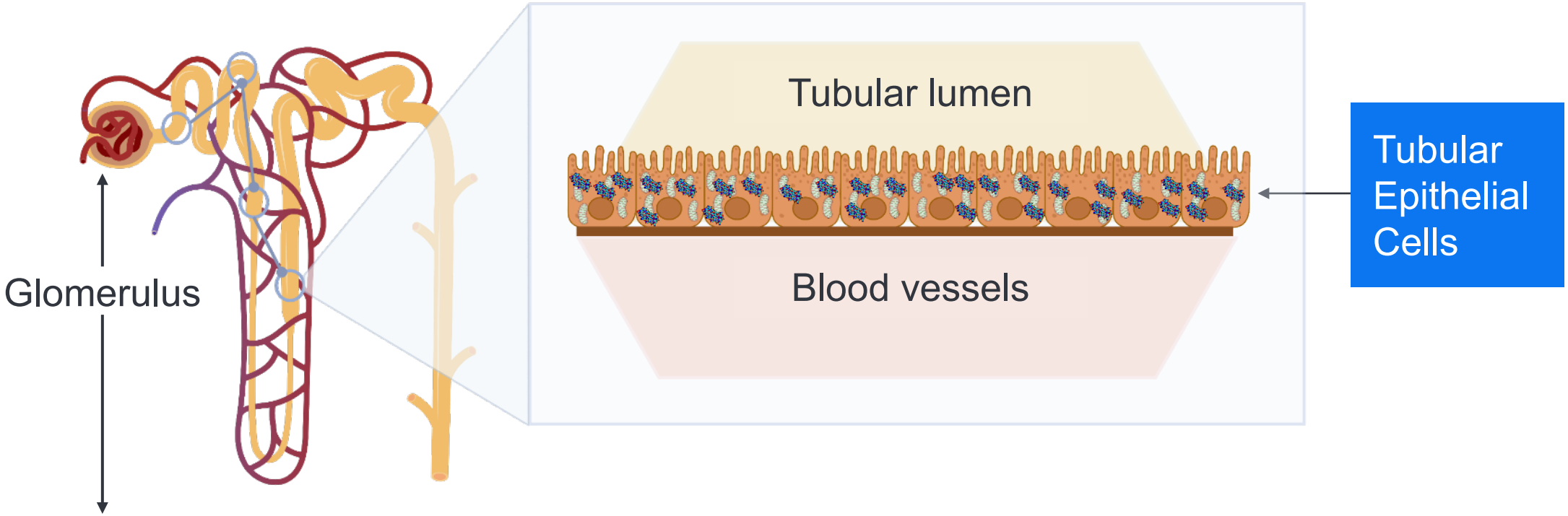
Demonstrates ongoing injury to the kidney independent of function, capturing early or insidious damage



References
1. Hall JA, Yerramilli M, Obare E, Yerramilli M, Yu S, Jewell DE. Comparison of serum concentrations of symmetric dimethylarginine and creatinine as kidney function biomarkers in healthy geriatric cats fed reduced protein foods enriched with fish oil, L-carnitine, and medium-chain triglycerides. Vet J. 2014;202(3):588–596. doi:10.1016/j.tvjl.2014.10.021
2. Hall JA, Yerramilli M, Obare E, Yerramilli M, Almes K, Jewell DE. Serum concentrations of symmetric dimethylarginine and creatinine in dogs with naturally occurring chronic kidney disease. J Vet Intern Med. 2016;30(3):794–802. doi:10.1111/jvim.13942
3. Hall JA, Yerramilli M, Obare E, Yerramilli M, Jewell DE. Comparison of serum concentrations of symmetric dimethylarginine and creatinine as kidney function biomarkers in cats with chronic kidney disease. J Vet Intern Med. 2014;28(6):1676–1683.
4. Nabity MB, Lees GE, Boggess MM, et al. Symmetric dimethylarginine assay validation, stability, and evaluation as a marker for the early detection of chronic kidney disease in dogs. J Vet Intern Med. 2015;29(4):1036–1044. doi:10.1111/jvim.12835

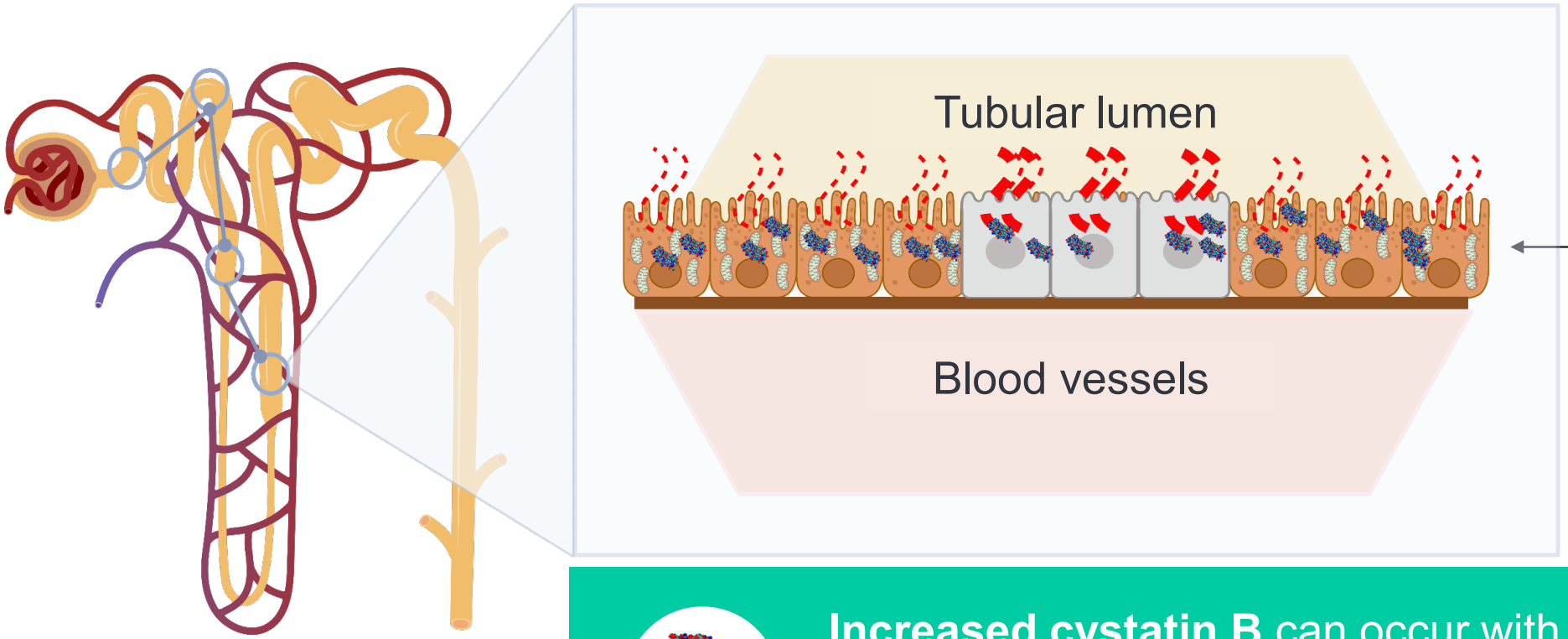
Cystatin B is a very small protein that is contained in the epithelial cells of the renal tubules.



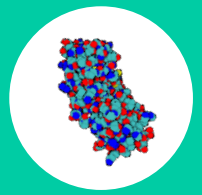


Decline in GFR measured by SDMA and
Creatinine at respectively 40% and 75% loss of function

During **Active or Acute Injury** to the kidney, the cells along the lining of the tubule system (responsible for secretion and reabsorption of solutes and water) can be damaged or necrotic.

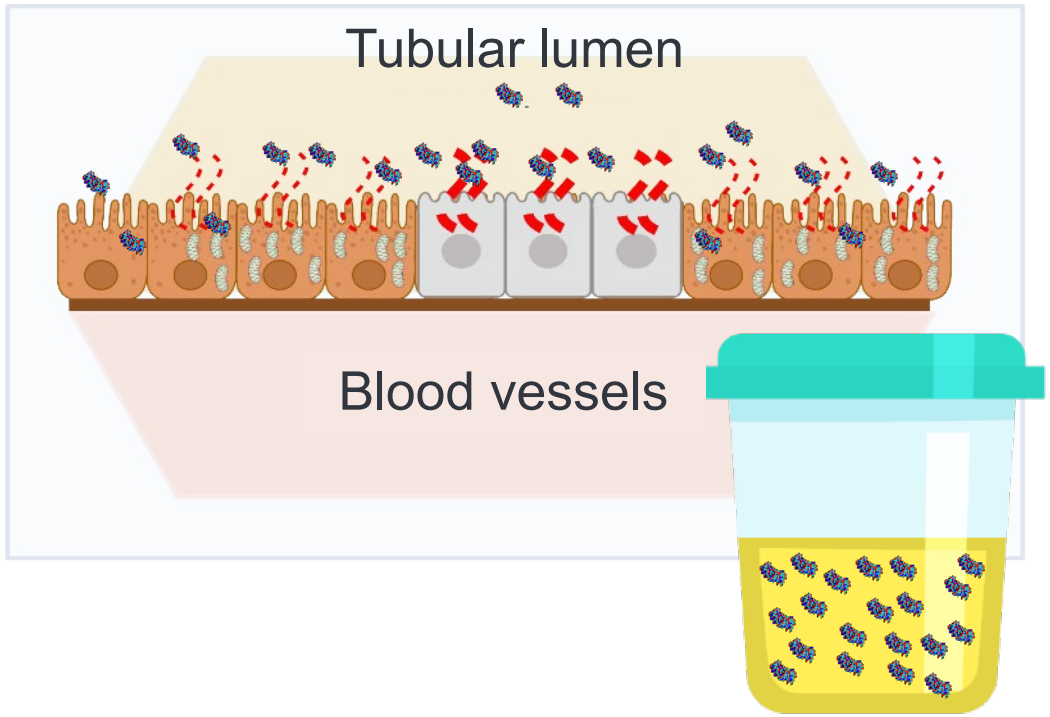


Cystatin B leakage from injured or necrosed tubular epithelial cells



Increased cystatin B can occur with or without functional marker increase, **alerting to earlier, ongoing, and unresolved** injury to the kidney.

The types of active and acute injury that can cause cystatin B to leak into urine include both primary and secondary insults to the kidney.



1

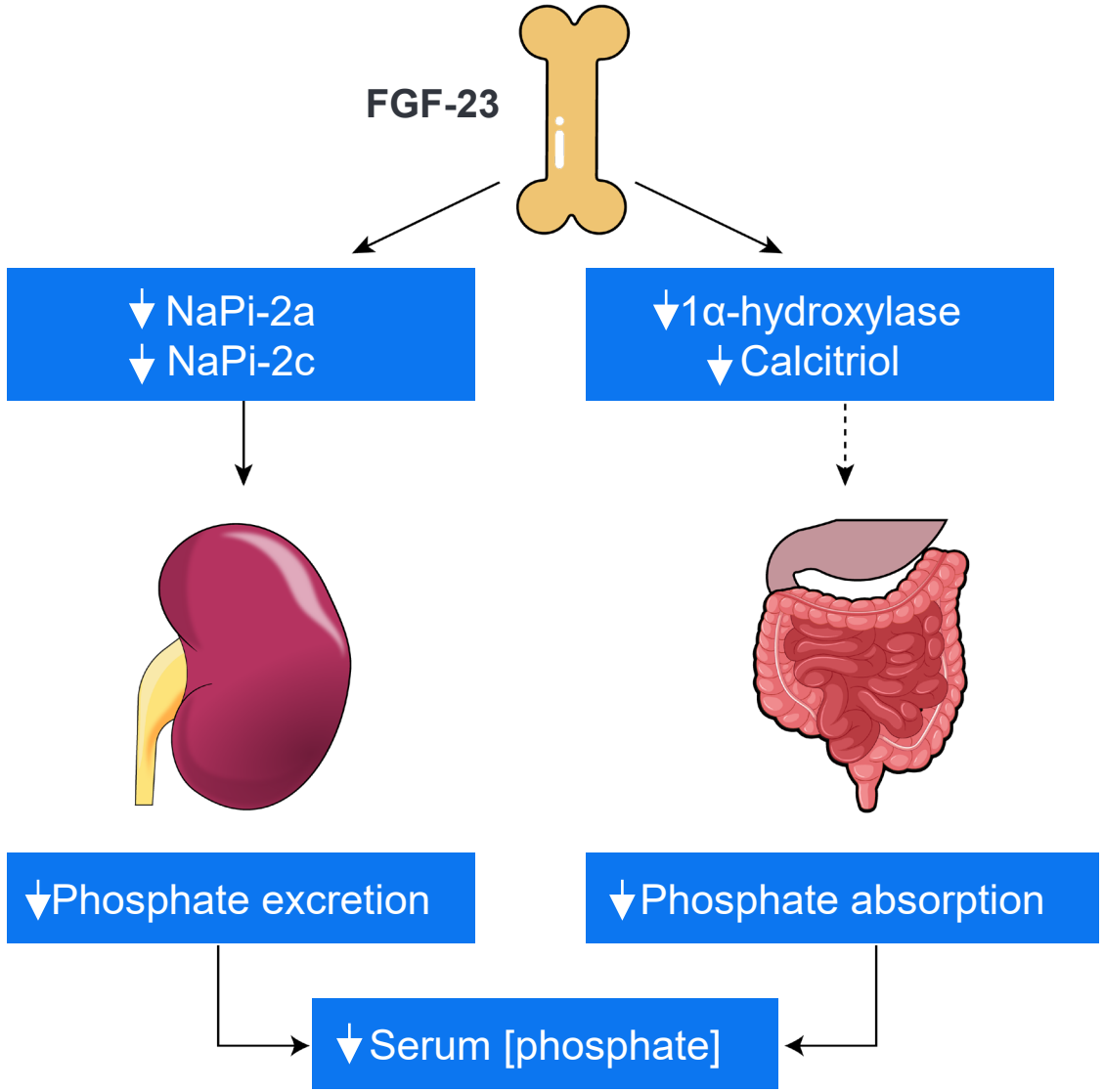
+ Primary nephritis
+ Immune-mediated disease
+ Chronic kidney disease

2

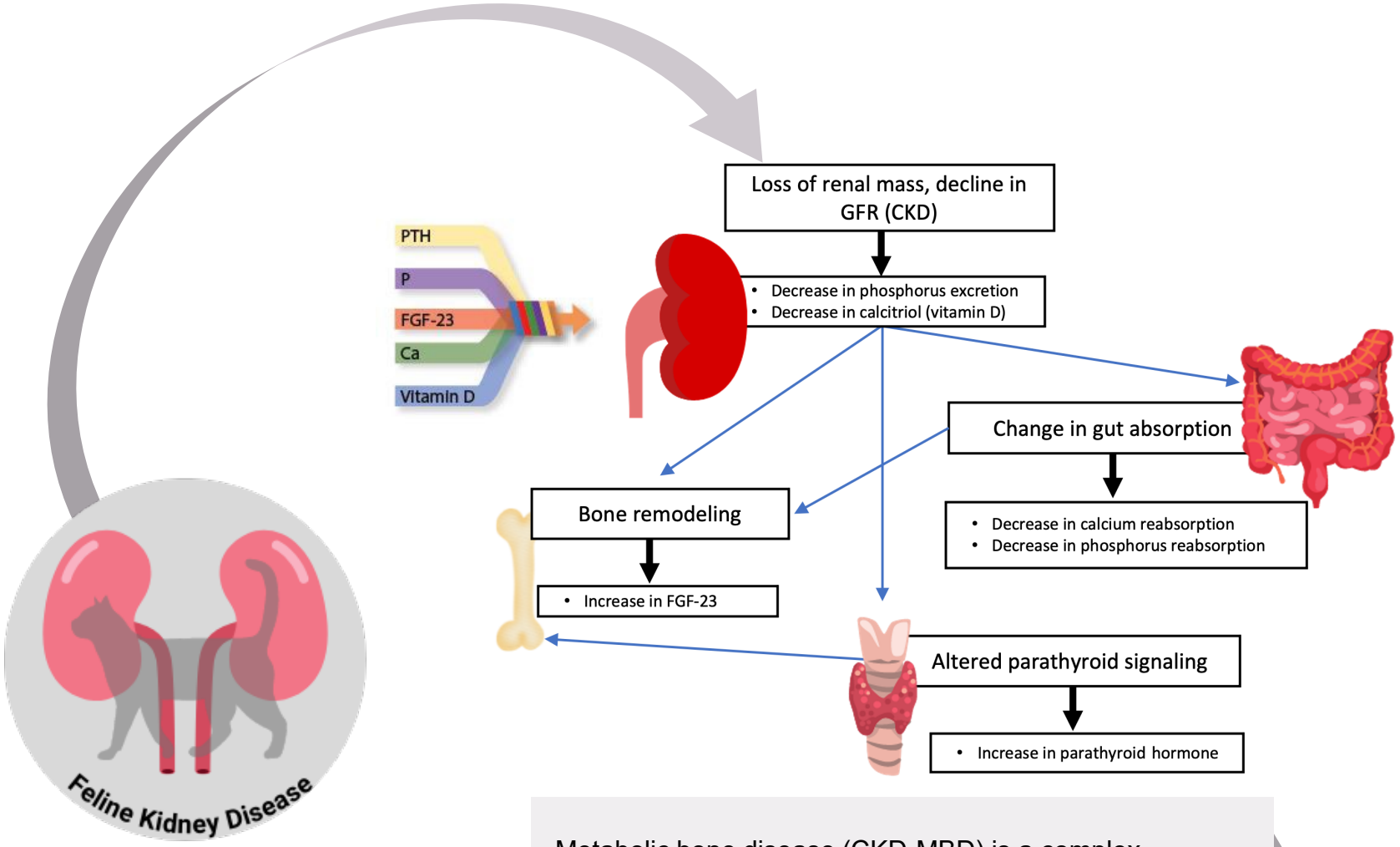
+ Pyelonephritis
+ Vector-borne infectious disease
+ Toxic insult
+ Systemic inflammatory disease (pancreatitis, vasculitis)

Fibroblast growth factor-23 (FGF-23)

- Phosphatonin—hormone regulating phosphate balance
- Released from osteocytes in response to increased phosphorus, calcitriol, and PTH concentrations
- FGF-23 decreases phosphorus and calcitriol concentrations
- Important in animals with chronic kidney disease
- Clinical measurement is now commercially available and indicated for animals with kidney disease (impaired phosphate excretion)



When should the IDEXX FGF-23 Test be run?

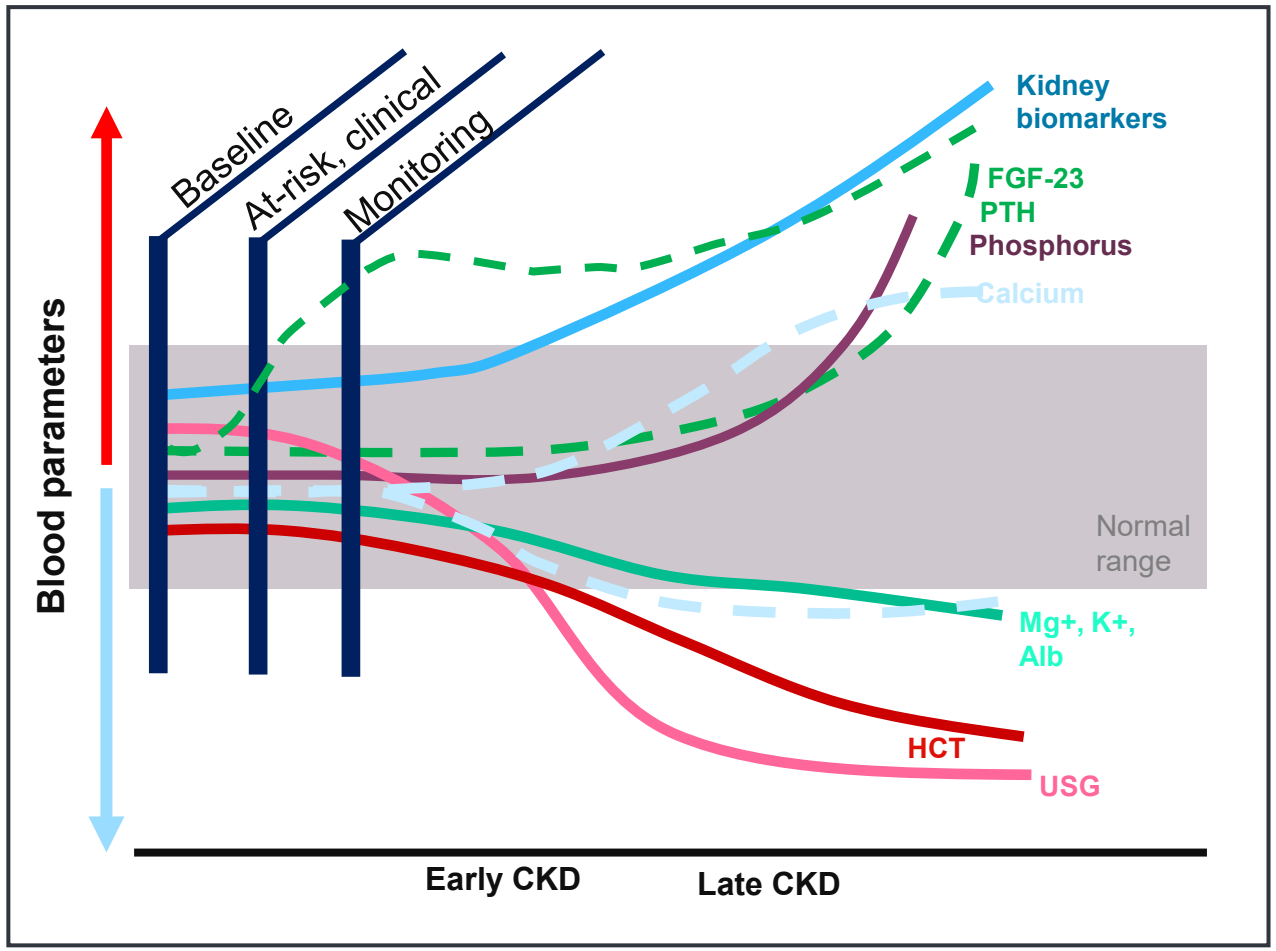


FGF-23 is released in response to increases in phosphorus and calcitriol

FGF-23 often rises before total serum phosphorus alerting earlier need phosphorus reduction

Metabolic bone disease (CKD-MBD) is a complex syndrome that involves fibroblast growth factor-23 (FGF-23), parathyroid hormone (PTH), 1,25-dihydroxy D3 (1,25 vitamin D_3, calcitriol), calcium, and phosphorus

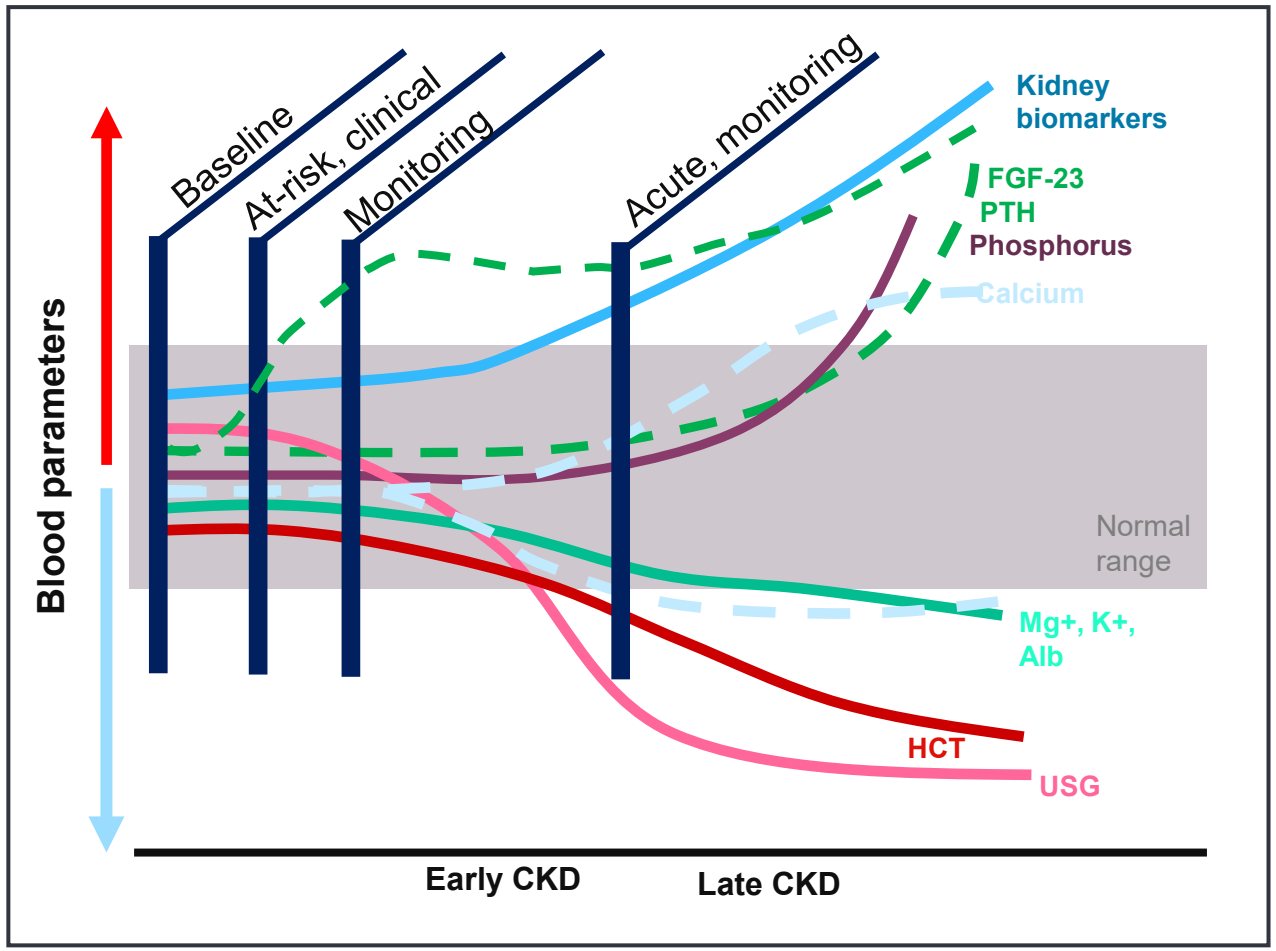
Monitoring is part of therapy: how many time points set us up for success?



Trending

1. Baseline, understand the patient
2. Trend, positive and negative—suspicion, clinical context
3. Story, decision point and pattern understanding

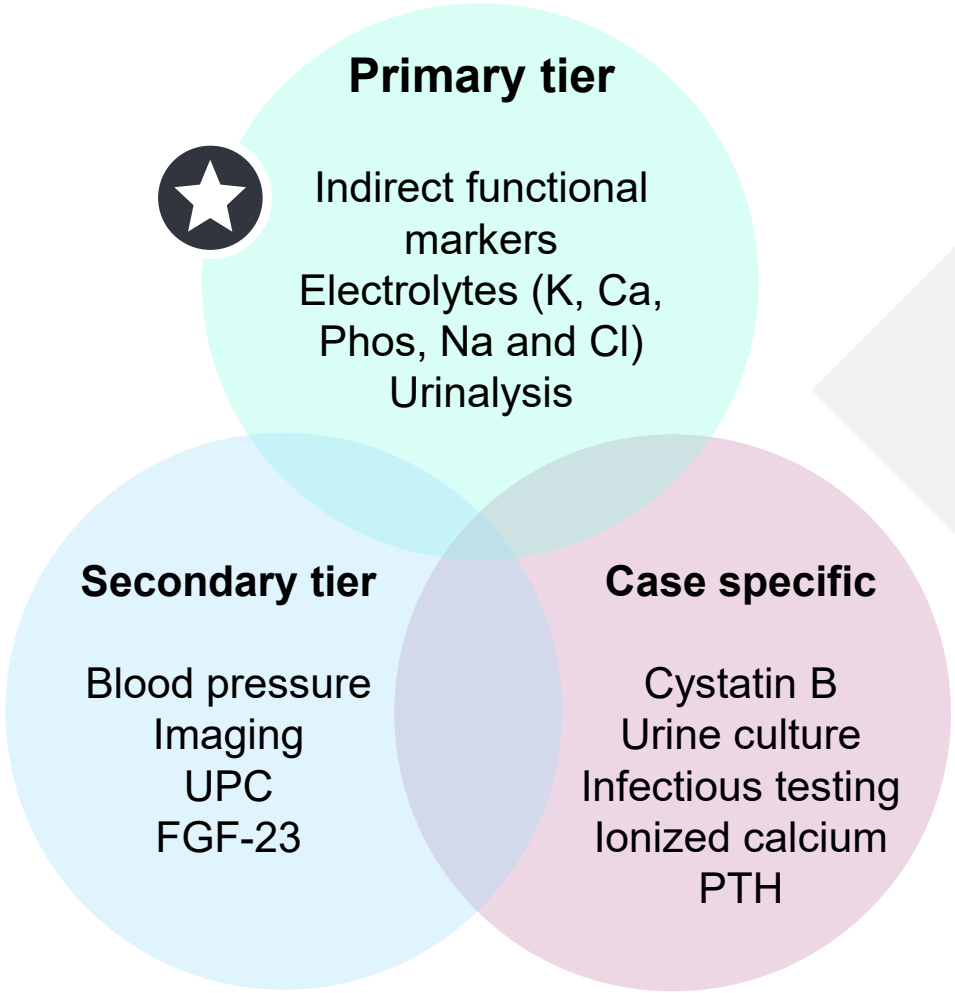
Monitoring is part of therapy: how many time points set us up for success?



Trending

4 Baseline, understand the patent

Where, when, and what diagnostics are appropriate?



Diagnostics

Kidney disease

Metabolic bone disease
Cardiorenal syndrome
Anemia - iron deficiency
Cachexia
Other comorbidities

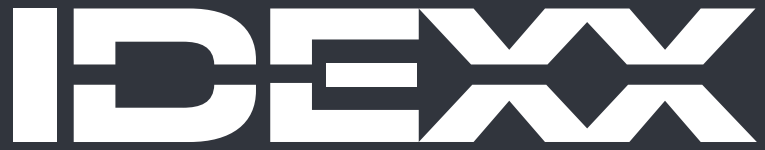
Sequelae

IDEXX is green

Please project (don’t print) this presentation.

Thank You.

IDEXX


IDEXX